

REMARKS

A. Status of the Claims

Claims 1-3 were originally filed with the case on May 12, 2005. Claims 1-3 were rejected in an Official Action mailed on November 30, 2006. No claims were amended, added, or canceled in the Response to Office Action filed on March 30, 2007. Claims 1-3 are rejected in the present Office Action. No claims are amended, added, or canceled herein. Applicants thank the Examiner for the previous consideration of our submissions.

B. The Claims are Patentable Over Malfroy-Camine in view of Winkler

The Action rejects all claims under 35 U.S.C. 103(a) as being obvious over Malfroy-Camine et al. (6,064,188) in view of Winkler et al. (Molecular Vision 1999). Malfroy-Camine is said to teach the antioxidant and superoxide dismutase activity of the claimed compounds. Winkler is said to teach the role of oxidation in relation to macular degeneration and suggest that superoxide dismutase activity may be involved in preventing oxidative damage. The Action suggests that the combination of these references would have made obvious to one skilled in the art the use of the claimed compounds having superoxide dismutase activity for the treatment of conditions associated with oxidative damage such as AMD. Applicants respectfully traverse.

Determining obviousness requires an analysis of the invention *as a whole*. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990). It is well settled patent law that “obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” *See In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01.

In addition, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91

The combination of the cited references does not teach or suggest the claimed invention, nor is there any teaching, suggestion, or motivation in these references that would produce the claimed invention. The present invention is directed to the use of mimics of the enzyme superoxide dismutase to treat persons suffering from the exudative and non-exudative forms of AMD, diabetic retinopathy, which includes proliferative diabetic retinopathy, and retinal edema. While Malfroy-Camine does recognize that the claimed compounds exhibit antioxidant and superoxide dismutase activity, Winkler does not teach or suggest that the compounds of Malfroy-Camine can be used for the treatment of macular degeneration, diabetic retinopathy or retinal edema.

The Action cites Winkler as teaching the role of oxidation in relation to macular degeneration and suggesting that superoxide dismutase activity may be involved in preventing oxidative damage. Applicants respectfully argue that, based on the entirety of the prior art available at the time the invention was made, there was no reasonable expectation of success for using superoxide dismutase for treating macular degeneration based on Winkler, and the invention is therefore not obvious.

An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *KSR Intn'l Co. v. Teleflex Inc.*, No. 04-1350, 550 U.S. ____ (2007); *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). The Action states that obviousness does not require absolute predictability. However, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986).

At the time the present invention was made, Winkler was one of several references that discussed the potential role of superoxide dismutase in preventing oxidative damage and the correlation between oxidative damage and AMD. Winkler discusses superoxide dismutase only as one of a number of oxidants that may play a role in AMD progression. Superoxide dismutase is identified in Winkler as a potential protectant of molecules damaged

by oxidation, along with sunglasses and the series of non-enzyme antioxidants. Winkler focuses the majority of its discussion on studies involving these non-enzyme antioxidants including glutathione (GSH), vitamin C, vitamin E, and carotenoids. While the paper does suggest that superoxide dismutase may be involved in preventing oxidative damage, it provides no methodology for how superoxide dismutase could be used to treat macular degeneration nor does it provide any research to support its assertion that the enzyme may play a role in AMD progression.

Though Winkler did not provide research data to support its assertion, there were other references available at the time the invention was made that provided empirical evidence that there was no association between superoxide dismutase activity and AMD. Based on the lack of support provided by Winkler and the abundance of evidence given in the other controverting references, it should be clear that Winkler provided no reasonable expectation of success for using superoxide dismutase to treat macular degeneration.

Both De La Paz (British Journal of Ophthalmology 1996) and Delcourt (Ophthalmology 1999) involve research studies in which blood samples were taken from a group of participants in order to statistically analyze the levels of superoxide dismutase activity in comparison to the severity of AMD. The De La Paz study included 66 participants, 54 of whom showed varying levels of severity of aging maculopathy. The paper concluded based on multiple regression analysis and ordinal logistic regression analysis that there is no significant association between disease severity of AMD and superoxide dismutase activity. The Delcourt study included 2,156 participants for its analysis of AMD and antioxidant enzymes, 38 of whom had late AMD. The paper concluded, based on similar statistical analyses, that high levels of erythrocyte superoxide dismutase activity were not associated with late AMD and early signs of AMD.

While both De La Paz and Delcourt acknowledged that oxidative mechanisms may play a role in the development of AMD and that superoxide dismutase is involved in protecting against such oxidative damage, each provided statistical data that higher levels of the enzyme do not affect the severity of AMD. Like Winkler, neither of these references showed that superoxide dismutase could be used to treat macular degeneration. Although the references recognize that superoxide dismutase is involved in protecting against oxidative damage such as that which potentially leads to AMD, there is no indication that higher levels of the enzyme could be used to treat the disease. In fact, these papers seemed to suggest that

an increase in the amount of the enzyme would have no effect because there is no association between the severity of AMD and the amount of superoxide dismutase activity. Thus, these papers appear to teach away from the use of superoxide dismutase for treating macular degeneration. Winkler does not provide or discuss any data that refutes the data or conclusions in De La Paz or Delcourt. Consequently, one of skill in the art would not have been motivated to use compounds with superoxide dismutase activity for treating macular degeneration, since there would have been no reasonable expectation that the use of such compounds for that purpose would be successful.

In order to support a 103 rejection of the instant claims, the cited references must teach or suggest a method for treating AMD, DR, and/or retinal edema via administration of the described compounds. The combination of the cited references does not teach or suggest that the administration of the salen-metal complexes described in the instant specification would effectively treat AMD, DR, and/or retinal edema. In addition, the combination of cited references does not provide evidence for a reasonable expectation of success for using such compounds for treating AMD, DR, and/or retinal edema at the time the invention was made.

In light of the foregoing arguments, Applicants respectfully request that the obviousness rejection be withdrawn.

C. Conclusion

This is submitted to be a complete response to the outstanding Action. The Examiner is invited to contact the undersigned attorney at (817) 615-5330 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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